Published in final edited form as:

Prog Pediatr Cardiol. 2016 March ; 40: 21–23. doi:10.1016/j.ppedcard.2016.01.007.

Integrating Genetics and Medicine: Disease-Modifying Treatment Strategies for Hypertrophic Cardiomyopathy

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Introduction

Hypertrophic cardiomyopathy (HCM) was the first inherited cardiomyopathy characterized at the molecular level.^{1, 2} Approximately 25 years have elapsed since landmark genetic studies demonstrated that sarcomere mutations cause disease. In that time, genetic testing has evolved from residing strictly in the realm of research performed at a small number of laboratories, to becoming a commercially-available test used in clinical practice. Genetic testing now routinely identifies disease-causing (pathogenic) sarcomere mutations in patients with HCM. Through family testing, we can also identify “preclinical” mutation carriers. These relatives have inherited the mutation that causes HCM in their family and are therefore at risk for developing disease, but currently have normal left ventricular wall thickness and no diagnostic clinical manifestations. This intriguing population provides not only a valuable opportunity to study early phenotypes of sarcomere mutations, but also a key target for novel disease-modifying therapy. By better understanding how sarcomere mutations lead to the complex phenotype of HCM, we hope to ultimately develop therapies that can interrupt disease-initiating pathways, thereby slowing or preventing the emergence of disease. The possibilities and challenges facing disease-modifying therapy are discussed in this article.

Background

Hypertrophic cardiomyopathy is defined clinically by the presence of “unexplained” left ventricular hypertrophy (LVH); increased left ventricular wall thickness that is not easily explained by pressure overload or infiltrative processes. In addition to hypertrophy, the pathological hallmarks are myocyte disarray and fibrosis. The most common clinical manifestations include exertional dyspnea, chest pain, and arrhythmias. Although the majority of patients will experience normal longevity and manageable symptoms, serious outcomes are associated with HCM, including sudden cardiac death and refractory heart

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failure. The estimated prevalence in the general population is roughly 1:500 to 1:1000, predicting up to 600,000 cases in the United States.³

Familial disease with autosomal dominant inheritance of HCM has been recognized for many years. Seminal genetic studies in the 1980s and 1990s established that HCM is a disease of the sarcomere—frequently caused by mutations in genes encoding different components of the molecular motor of the heart.² Sarcomere mutations can be identified in ~30% of all-comers with a clinical diagnosis of HCM. If familial disease is present, sarcomere mutations are identified in ~60% of cases. Mutations in cardiac β -myosin heavy chain (*MYH7*) and myosin binding protein C (*MYBPC3*) are most common; collectively responsible for over 80% of HCM due with an identified genetic cause.⁴

Despite this exquisite knowledge of the molecular basis of disease, our current approach to treating patients with HCM remains quite crude. For patients with clinically overt disease, management is focused on palliating symptoms and assessing risk for sudden cardiac death to determine if an implantable cardioverter-defibrillator (ICD) should be placed. For preclinical sarcomere mutation carriers at risk for developing HCM, our approach is largely passive and reactionary. Individuals are followed with serial clinical evaluation to document the development of LVH that would trigger a diagnosis of HCM. However, we are unable to predict when, or even if, disease will develop, or how severe it will be.

New Paradigms for Clinical Care: Aspirations for the Future

By improving our understanding how sarcomere mutations cause HCM, we hope to develop better, more rational and mechanistic treatment strategies. These new strategies will focus on identifying and targeting early, disease-initiating pathways in order to diminish and prevent the emergence of HCM, rather than merely palliating symptoms once disease has already become entrenched. Studying the unique population of preclinical sarcomere mutation carriers, prior to diagnosis with HCM, may provide insights regarding early stages of disease development. Such studies will help to identify early phenotypes of sarcomere mutations, isolating changes caused primarily by the mutation from the confounding effects related to overt disease.

Cross-sectional studies on preclinical mutation carriers have helped to a number of early phenotypes of sarcomere mutations. Impaired left ventricular relaxation,⁵ altered myocardial energetics,⁶ ECG abnormalities,⁷ mitral valve abnormalities,⁸ myocardial crypts,⁸⁻¹¹ and evidence of a profibrotic state,^{12, 13} can be detected in the absence of clinically evident HCM, indicating that sarcomere mutations can cause subtle abnormalities even when LV wall thickness is normal. However, many key questions and limitations remain. None of these early phenotypes are perfectly sensitive for the presence of a sarcomere mutation. Preclinical mutation carriers are very difficult to distinguish from healthy controls using current technology with relatively crude phenotyping tools. Because longitudinal data are extremely sparse, it is unclear how early phenotypes relate to the future development of clinically overt disease. Nevertheless, it is possible that these early phenotypes may serve as a reliable monitor for disease progression, and thereby provide surrogate endpoints to gauge treatment response in clinical trials of disease-modifying therapy. Moreover, just the

presence of a preclinical state has intriguing implications because it indicates that it is possible to coexist with a sarcomere mutation, often for long periods of time, without overt disease. Because the mutation does not immediately cause irreversible manifestations, disease-modifying therapy that prolongs the preclinical phase may be both feasible and beneficial.

Early Phenotypes and Prototypes for Disease Modification

Animal models of HCM have been developed where sarcomere mutations that cause human disease are introduced into genetically-modified mice.¹⁴ These mice display an appropriate phenotype, developing myocardial hypertrophy, disarray, and fibrosis in an age-dependent manner. Based on studies showing that altered intracellular calcium handling is an early feature of disease pathogenesis,¹⁵ the effect of pharmacologic agents that alter calcium handling was tested. In these mouse clinical trials, administration of the L-type calcium channel blocker diltiazem showed promising results. Young animals started on diltiazem at an early age, prior to the development of LVH, showed attenuated phenotypic progression compared to placebo-treated animals.¹⁶ Diltiazem-treated mice developed less prominent LVH, less myocardial fibrosis, and had improved intracellular calcium handling. These studies suggest a mechanistic link between calcium handling, LVH and fibrosis. The clinical implications are exciting--indicating that early pharmacologic treatment may improve the natural history of genetic heart disease.

Based on these findings, we recently completed a pilot placebo-controlled, double blind randomized clinical trial testing the safety and feasibility of diltiazem treatment for early human HCM.¹⁷ In this trial, 38 sarcomere mutation carriers without LVH (mean age 15.8 ± 8.6 years; 58% female) were randomized to receive blinded therapy with diltiazem or placebo for a median duration of 25 months. This trial was among the first of its kind to test genotype-guided disease modification in genetically susceptible individuals, prior to the development of clinical disease. It demonstrated that diltiazem was safely administered to a young, healthy population without significant adverse effects.

It was difficult to identify a clear treatment response given limitations of study size, duration, and tools for phenotyping. However, there was a suggestion that diltiazem may attenuate a longitudinal decrease in LV cavity size in preclinical HCM sarcomere mutation carriers. This result is notable because small LV cavity size is a consistent feature of HCM. Even in the absence of LVH, trial participants had small LV cavities, with a mean LV end-diastolic dimension z-score of -1.5 at study entry. LV cavity size increased towards normal in diltiazem-treated participants, but continued to decrease in those treated with placebo, independently of changes in heart rate or blood pressure. Additionally, the ratio of LV thickness and dimension decreased slightly in the diltiazem group and increased in the placebo-treated group. Reducing the ratio of LV wall thickness and dimension is predicted to improve ventricular compliance through purely geometric effects, even if there are no changes to the myocardium itself. Finally, subjects who carried *MYBPC3* mutations appeared to have more striking benefits from diltiazem, showing improvements in LV wall thickness, mass, diastolic parameters, and serum cardiac troponin levels. These results

highlight the potentially important influence of genetic background on treatment response when using such targeted or “personalized” approaches.

Subsequent studies on HCM mouse models have highlighted an important role of transforming growth factor- β (TGF- β) activation in disease pathogenesis, particularly the development of fibrosis.¹⁸ Moreover, inhibiting TGF- β activation, either with neutralizing antibody or through administration of the angiotensin II receptor blocker (ARB), losartan, diminished disease emergence. A multicenter, randomized clinical trial is now underway in human HCM to test whether the ARB, valsartan, is able to attenuate disease evolution in early sarcomeric HCM (VANISH trial, ClinicalTrials.gov identifier NCT01912534).

Potential Opportunities and Challenges Facing Disease-Modifying Treatment Strategies

As understanding of disease pathogenesis improves, we hope to continue developing and testing novel treatments that are intended to diminish phenotypic evolution. The ultimate hope is to one day be able to prevent the emergence of disease all together. Such treatment strategies will target early pathways that play a key role in disease evolution. An advantage of this approach is that treatment to delay or prevent disease may be more feasible biologically than trying to reverse or rescue severe changes after entrenched, late-stage disease has developed. Indeed, the mouse studies described above suggested that disease-modifying treatment was ineffective when started after a clinical phenotype had already been established.^{16, 18} With the increased accessibility of genetic testing, we can now identify at-risk sarcomere mutation carriers early in life, during this potentially modifiable stage of disease.

However, clinical trials that test novel disease-modifying strategies face daunting challenges. For example, both the onset and expression of disease are unpredictable and heterogeneous. Although the pathogenic sarcomere mutation is present from birth, clinically overt HCM may not develop for decades. Some individuals may not develop disease at all, or have only very minor consequences. Owing to the marked variation in disease course, the optimal timing of treatment is unclear. Who should be treated and when should treatment be started? Will lifelong therapy be needed to inhibit phenotypic progression? Moreover, although HCM can be associated with devastating outcomes, the event rate in the overall patient population is relatively low, especially if healthy preclinical mutation carriers are included as trial participants. Consequently, trials will have to consist of large cohorts followed over long periods of time to demonstrate treatment benefit as reflected by traditional outcomes, such as mortality or the development of clinically overt disease. Successful execution of trials of such scope and scale will require monumental effort, particularly since sarcomeric HCM is relatively rare.

Because of these challenges, traditionally-designed clinical trials are unlikely to be successful. In order to complete early phase, test-of-concept trials with feasible time frames and cohort sizes, we will need to identify appropriate surrogate endpoints. Such endpoints will accurately reflect disease progression and treatment benefit, and will have a greater chance of showing dynamic change over shorter periods of time. Robust, quantitative early

phenotypes that reflect a continuum of disease progression from normal controls to patients with overt disease may be valuable in this regard. Effective treatment would then potentially demonstrate that mutation carriers with early disease become more “normal” for the metrics under study. In parallel with these efforts, we also need to identify more accurate predictors of adverse outcomes.

Next, choosing which individuals to target and how long to treat will require thoughtful consideration. Directing therapy towards the youngest mutation carriers without any phenotypic expression may be unproductive, as disease progression may not occur over the short terms that typical trials are conducted. It may not be possible to demonstrate treatment benefit in less than 10 years of follow-up. Therefore, it may be best to focus initial trials of disease modification on mutation carriers with mild phenotypic expression, refining patient selection as knowledge grows regarding both early phenotypes and pathways governing disease evolution.

Finally, more innovative statistical analysis plans are needed to reduce the risk of false negative trial results, without excessively increasing the risk of false positive results.¹⁹ Experience gained from initial trials of disease modifying therapies will provide a crucial foundation to plan more definitive trials.

Summary

Hypertrophic cardiomyopathy is an intriguing and complex disease. Our current management focuses on symptom palliation, sudden death risk assessment, and surveillance for disease development. Looking to the future, integrating genetics into medicine has tremendous potential to improve both clinical practice and fundamental understanding of disease. Genetic testing allows early identification of at-risk relatives before a clinical diagnosis can be made. This provides the opportunity to initiate disease-modifying therapy at a time when it may be most successful. Longitudinal study of genotyped populations will provide critical insights regarding disease progression and determinants of adverse outcomes. With greater knowledge of pathogenesis, we hope to develop proactive, disease-modifying treatment strategies that will delay and ultimately prevent the emergence of HCM. Moreover, we hope to be able to target these therapies to those at greatest risk and who will therefore receive the greatest benefit. With such advances, genetic discoveries will begin to meet their full potential to change the practice of medicine.

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